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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,334	01/16/2004	Steven C. Pruitt	03551.0149	7276

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EXAMINER	
LONG, SCOTT	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,334	PRUITT ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-19 are pending. Claims 1-16 are amended. Claims 17-19 are newly submitted. Claims 1-19 are under current examination.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 24 November 2006 consisting of 1 sheet(s) are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from provisional U.S. Application No. 60/559,209, filed 1 April 2004. The instant application has been granted the benefit date, 1 April 2004, from the application 60/559,209.

Response to Arguments - Claim Rejections 35 USC § 102

Applicant's arguments (Remarks, page 7) filed 16 July 2007 have been fully considered and they found to be persuasive.

The applicant argues that Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088) do not teach the more narrowly amended claim 1

wherein the cell lineage targeting vector comprises cell lineage specific promoters placed upstream of the recombinase recognition sites. (Remarks, page 7).

The examiner finds this argument persuasive and therefore withdraws the rejection of claims 1-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088).

Response to Arguments - Claim Rejections 35 USC § 103

Applicant's arguments (Remarks, pages 7-8) filed 16 July 2007 have been fully considered and they found to be persuasive.

The applicant argues that Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088) is defective in disclosing the invention recited in the instant independent claims and that the supplemental references also do not teach this limitation.

The examiner finds this argument persuasive and therefore withdraws the rejection of claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088) in view of Zambrowicz et al. (Int.J.Dev.Biol. 1998; 42: 1025-1036) and further in view of Velculescu et al. (Science. 20 October 1995: 484-487).

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorey et al. (Molecular and Cellular Biology. May 1998. Vol.18, No.5: 3081-3088) in view of Zambrowicz et al. (Int.J.Dev.Biol. 1998; 42: 1025-1036) and further in view of Velculescu et al. (Science. 20 October 1995: 484-487) and further in view of Wan et al. (Journal of Molecular Endocrinology. 2002. 28: 177-192).

The claimed invention is directed to a method for identifying genes expressed during differentiation of a cell comprising the steps of: a) integrating into a site in the genome of a host cell, a cell lineage targeting vector comprising, a pair of recombinase recognition sites flanking one or more polyadenylation sites, a first selectable marker placed downstream of or between the two recombinase recognition sites, a reporter gene placed downstream of the recombinase recognition sites, and a cell lineage specific gene promoter placed upstream of the recombinase recognition sites or a cell specific lineage gene placed downstream of the recombinase recognition sites, b) amplifying cells generated from the host cell; c) integrating into the genome of a plurality of the amplified cells, a gene-trap vector comprising a splice acceptor, a type IIS restriction endonuclease cleavage site, a recombinase, one or more polyadenylation sites, a second selectable marker and a splice donor; d) allowing the cells to differentiate; e) isolating cells in which the reporter gene is expressed indicating expression of the cell lineage specific gene; f) identifying trapped genes in the isolated cells. The claimed invention also incorporates elements of modified serial analysis of gene expression (SAGE), particularly type IIS endonuclease sites and Assay Tags.

The teachings of Thorey et al. are summarized below:

Thorey et al. teach, "a strategy employing gene trap...and site-specific recombination (Cre.loxP) has been used to identify genes that are transiently expressed during...development. Thorey et al. teach diagrams (Fig.1, page 3082), that show a system of two vectors. One of the vectors comprises a pair of recombinase recognition sites (loxP) flanking one polyadenylation site, a selectable marker (Neo) placed

between the recombination sites, a reporter gene (lacZ) downstream of the recombination sites. The other vector comprises cellular promoter and a trapped gene flanked by recombination recognition sites (Cre). Thorey et al. describe isolating cells derived using their system (pages 3082-3083). Thorey et al. teach, that their system is "useful for demarcating cell lineages and for tracking cell fate and migration in the developing embryo." (page 3087).

Claim 2 is directed to the method of claim 1 wherein the trapped genes are sequenced. Thorey et al. teach sequencing of genes, using plasmids (concatamers).

Claim 3 is directed to the method of claim 2, wherein inverse PCR is used. Thorey et al. teach "inverse PCR" (page 3082).

Claim 4 is directed to the method of claim 2, wherein RT-PCR is used. Thorey et al. utilize rapid amplification of cDNA ends (RACE). Accordingly, the cDNA was derived from RNA and needed to be reverse transcribed.

Claim 5 is directed to the method of claim 1, wherein the step of identifying the trapped genes in step f) comprises the steps of: a) preparing mRNA from cells in which the fluorescent reporter is expressed in d); b) synthesizing a first and second cDNA strands from the mRNA; c) digesting with type IIS restriction endonucleases to produce Assay Tags wherein each Assay Tag comprises a portion of a trapped gene and a portion of the gene-trap vector; d) concatenating the Assay Tags; e) amplifying and sequencing the concatamers to identify the sequence of the portion of the trapped gene. Thorey et al. teach, selection of clones, isolation of cellular RNA, followed by RACE (page 3084, footnotes of Table 1). These steps comprise the sequence strategy of

Thorey et al. According to Thorey et al. "all sequences showed typical cell DNA-provirus junctions" (page 3085), indicating that the region sequenced contained both the trapped sequence and the gene-trap vector.

Claim 10 is directed to the method of claim 1, wherein the recombinase is Cre or FLP. Thorey et al. teach Cre recombinase.

Thorey et al. does not specifically teach use of the SAGE technique with gene trapping. Furthermore, Thorey et al. does not teach targeting vectors comprising gene promoter placed upstream of the recombinase recognition site.

Zambrowicz et al teach however, teach the use of SAGE with gene trapping techniques (page 1026). Zambrowicz et al. discuss the usefulness of combining gene trap and SAGE techniques for "high through-put methods...used for studying expression patterns of large numbers of genes at the RNA [level]." (page 1026) In particular, Zambrowicz et al. describe the utility of gene traps for identifying genes expressed during differentiation. Zambrowicz et al. also teach alternative selection techniques comprising the use of thymidine kinase fusion proteins (page 1030, col.1), satisfying the claim limitations of claims 11 and 21.

The details of SAGE are discussed in Velculescu et al., including the use of type II restriction sites and assay tags. Velculescu et al. also teach biotinylated DNA, as per the limitations of claims 6 and 16.

Wan et al. teach, "identification of genes differentially regulated by glucocorticoids and progestins using a Cre/loxP-mediated retroviral promoter-trapping strategy" (page 177, title). Wan et al. teach, "recombinants...are expressed from

hormone-inducible upstream cellular promoters....Thus this system permits the identification of genes that are transiently or weakly induced by hormone." (abstract. Page 177). Figure 2 (Page 182) illustrates construction of a vector comprising glucocorticoid- or progesterone-inducible promoters upstream of recombinase recognition sites and used for their promoter trap system. By placing the hormone receptor promoters upstream of the recombination sites, Wan et al. have produced a system while will allow determination of the expression pattern of hormone-regulated genes.

It would have been obvious to combine the promoter-trapping strategies of Wan et al. with the systems of Thorey et al. and Zambrowicz et al. and Velculescu et al. to produce a method for identifying genes expressed during differentiation of a cell. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the use of gene traps and serial analysis of gene expression. In addition, a skilled artisan would find it obvious to utilize an enhanced green fluorescent protein (as in claims 8-9 and 18-19) as a functional equivalent of β-galactosidase in the systems described by Thorey and Zambrowicz.

The person of ordinary skill in the art would have been motivated to make those modifications because "gene trapping combined with methods to monitor induction of expression of the trapped gene have now been used in a variety of cell types" (Zambrowicz, page 1030) and Zambrowicz et al. suggest combining gene trap and SAGE techniques for "high through-put methods...used for studying expression patterns of large numbers of genes at the RNA [level]." (page 1026). Furthermore, combining

high throughput screening elements with gene trapping vectors is merely "making integral" the two known processes; the MPEP 2144.04 holds that this type of combination is obvious. The person of ordinary skill in the art would have been motivated to make those modifications because fluorescent proteins, such as Green Fluorescent Protein (GFP) are functionally equivalent to lacZ (β-galactosidase) systems and do not require further reagents, such as X-gal, for visualization, as is the case for β-galactosidase. Furthermore, a person of ordinary skill in the art would have been motivated to utilize cell lineage specific gene promoters (such as hormone-inducible promoters) to determine the expression pattern of hormone-regulated genes, because protesterone receptor gene is expressed early during differentiation of embryonic stem cells and expression during organogenesis is important for tisse-specific development, indicating the importance of such genes.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Thorey and Zambrowicz and Velculescu and Wan because each of these teachings generated successful results independently and there is no indication that the combinations of high throughput screening elements with gene trapping vectors would be unsuccessful.

Therefore the method as taught by Thorey et al. in view of Zambrowicz et al. and further in view of Velculescu et al. and further in view of Wan et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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